UNITED STATES ENVIRONMENTAL PROTECTION
WASHINGTON, D.C. 20460

HED DOC. NO. 014267

08/03/00

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: ***OXAMYL*** - **Amendment** to the Report of the Hazard Identification Assessment Review Committee dated 07/17/00 (HED Doc. No. 014242).

FROM: David G. Anderson, Toxicologist
Reregistration Branch II
Health Effects Division (7509C)

THROUGH: Elizabeth Doyle, Co-Chair
and
Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Christina Jarvis, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 103801

The only change made to this HIARC report is the data on Primary Skin Irritation in the Acute Toxicity Profile for Oxamyl (Section IX).

Committee Members in Attendance

August 15, 1996

Members present were: Karl Baetcke, William Burnam, Stephan Dapson, Brian Dementi, Karen Hamernik, Paul Lewis, Guruva Reddy, Esther Rinde, Clark Swentzel, and Rick Whiting. Member in absentia: None. Data were presented by Whang Phang and James Rowe. Mike Ioannou signed in the capacity of Branch Chief, Tox. Branch II.

June 8, 1999

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pamela Hurley, Mike Ioannou, Tina Levine, Susan Markis, Nicole Paquette, Kathleen Raffaele, Jess Rowland, P.V. Shah, and Pauline Wagner. Members in absentia: Karen Hamernik and Nancy McCarroll. Data were presented by Guruva B. Reddy of Reregistration Branch II. Also in attendance were Ken Dockter, John Punzi and Diana Locke from HED and Susan Jennings from SRRD.

July 15, 1999

Members present were: William Burnam, Virginia Dobozy, Karen Hamernik, Pamela Hurley, Mike Ioannou, Susan Markis, Nicole Paquette, Jess Rowland, P.V. Shah, and Pauline Wagner. Members in absentia: Tina Levine, David Anderson, Kathleen Raffaele and Nancy McCarroll. Data were presented by Guruva B. Reddy of Reregistration Branch II.

July 5, 2000

Members present were: William Burnam, Pamela Hurley, Jess Rowland, Tina Levine, David Nixon, Elizabeth Mendez, Yung Yang, Ayaad Assaad, Jonathan Chen. Members in absentia: Elizabeth Doyle. Data were presented by David G. Anderson of Reregistration Branch II.

Data Presentation:
and
Report Presentation

David G. Anderson
Toxicologist

I. INTRODUCTION

Oxamyl is a water soluble insecticide (nematicide/acaricide) registered for use on field crops, vegetables, fruits, and non-bearing trees. Therefore, risk assessments for occupational exposures are applicable. There is a potential for mixer/loader/applicator exposure to oxamyl sprays. The exposure routes for handler uses are via dermal and inhalation. There is currently no non-occupational exposure anticipated for oxamyl.

On August 15, 1996, the Health Effects Division RfD Peer Review Committee established an RfD of 0.0002 mg/kg/day based on the NOAEL of 0.2 mg/kg/day established in the rat developmental toxicity study and an Uncertainty Factor of 1000 for inter-species extrapolation, intra-species variation and a lack of neurotoxicity studies (Memorandum: Rick Whiting, HED to Dennis Edwards, RD dated November 5, 1996).

On June 8, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the existing RfD and established the toxicology endpoints for acute dietary, chronic dietary as well as occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act (FQPA) of 1996. The HIARC recommended the revisit of this chemical to address the potential enhanced sensitivity of infants and children as required by FQPA, since all the DERs were not available for review at the meeting.

In addition, on June 8, 1999, the HIARC evaluated recently submitted acute, and subchronic neurotoxicity studies in the rat, the 21-Day dermal toxicity study in rabbit and a rebuttal to a chronic dog study and a developmental toxicity study in the rat. Earlier, the endpoints for acute, and chronic dietary and short- and intermediate-term exposures were based on developmental toxicity in the rat and 21-day dermal toxicity study in the rabbit, respectively. The committee's conclusions are presented in this report. The report also notes that the chronic dog study (MRIDs 41697901, 42052701 & 44737503) is upgraded from supplementary to **Acceptable/guideline**. (HED DOC NO. 013711, dated August 31, 1999)

On July 15, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) assessed the susceptibility of infants and children to oxamyl as required by the Food Quality Protection Act (FQPA) of 1996.

On July 5, 2000, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reassessed the inhalation endpoint. The registrant submitted a new acute inhalation study with cholinesterase analyses (MRID# 45155801). The reassessment of the inhalation endpoint is contained in the following report.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: Acute Oral Neurotoxicity **Guideline #:** 81-8

MRID No.: 44254401, 44420301 & 44740701

Executive Summary: In an acute oral neurotoxicity study (MRID Nos: 44254401 & 44420301 & 44740701), single gavage doses of oxamyl (98.3% a.i.; Sample No.: 16995-02) in deionized water were administered to groups of Crl:CD rats (42/sex/dose). Males received 0, 0.1, 1.0, or 2.0 mg/kg and females received 0, 0.1, 0.75, or 1.5 mg/kg. Twelve rats/group were designated as neurotoxicity subgroup animals. All twelve of these rats/group were used for Functional Observational Battery (FOB) and Motor Activity (MA) assessments on days 1, 8, and 15. Body weight and clinical signs were also recorded for these animals. Six rats/group were euthanized for *in situ* perfusion. Thirty rats/group were designated as the clinical pathology group and were utilized for blood and brain collection for evaluation of cholinesterase levels.

One high-dose male died on day 1. High-dose males had significantly ($p<0.05$) decreased mean body weight gain for days 1-2. Similarly, mid-dose males and high-dose females also exhibited lower (n.s.) body weight gains. Decreased food consumption (n.s.) was also observed in mid- and high-dose males.

Statistically ($p<0.05$) and biologically significant dose related decreases in blood and brain cholinesterase activity were observed in mid- and high-dose males and females on day 1. Mean decreases were generally $\geq$40%. By day 2, decreases in cholinesterase activity were no longer biologically significant. No toxicologically significant decreases in cholinesterase activity were observed in any animals after day 1 or in low-dose males and females at any time point.

Clinical signs and FOB effects, consistent with decreased cholinesterase activity, were observed 30-60 minutes post-exposure in the mid- and high-dose males and females. Observations included soiled fur, lacrimation, salivation, slow righting reflex, abnormal gait, tremors, impaired locomotion, no response to tail pinch, limb splay, incoordination, labored breathing, and decreased forelimb and hindlimb grip strength. Other effects, including posture, palpebral closure, docile behavior, and decreased motor activity, were likely due

to lethargy and malaise secondary to decreased cholinesterase activity. No treatment-related clinical signs or FOB effects were observed in low-dose animals or after day 1. Therefore, **the RBC, plasma and brain ChE inhibition NOAEL = 0.1 mg/kg/day for males and females and LOAEL = 1.0 mg/kg/day in males and 0.75 mg/kg/day in females.**

No treatment-related gross effects or histopathology were observed.

Under the conditions of this study, **the systemic/neurotoxicity LOAEL is 1.0 mg/kg for male rats and 0.75 mg/kg for female rats based on clinical signs, FOB effects, and decreased blood and brain cholinesterase activity. The NOAEL** is 0.1 mg/kg.

This acute oral neurotoxicity study is classified **Acceptable/Guideline**. This study does satisfy the guideline requirement for an acute oral neurotoxicity study (81-8) in rats.

Dose Selected for Risk Assessment: NOAEL= 0.1 mg/kg based on plasma, red blood cell (RBC) and brain cholinesterase inhibition (ChEI) at 0.75 mg/kg (LOAEL).

Comments about Study/Endpoint: The HIARC noted the occurrence of a statistically significant decrease in ChE activity in the cerebellum of female rats at 0.1 mg/kg/day (the NOAEL). The Committee, however, concluded that the observance of ChEI at this dose does not constitute this to be LOAEL since the decrease was seen only in one section of the brain (cerebellum), in one compartment (no plasma or RBC ChEI) and in only one sex (no plasma, RBC or brain ChEI was seen in males at this dose) and there was no dose-response for this effect. Therefore, this dose (0.1 mg/kg) was considered to be the NOAEL.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variability).

$$\textbf{Acute RfD} = \frac{0.1 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.001 mg/kg}$$

B. Chronic RfD

The RfD established in 1996 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Study Selected: Acute Oral Neurotoxicity **Guideline #:** 81-8

MRID Nos.: 44254401, 44420301 & 44740701

Executive Summary: See acute dietary.

Dose Selected for Risk Assessment: NOAEL= 0.1 mg/kg based on plasma, red blood cell (RBC) and brain cholinesterase inhibition (ChEI) at 0.75 mg/kg (LOAEL).

Comments about Study/Endpoint: Ideally a NOAEL from the chronic study will be selected for establishing the chronic RfD. However, for Oxamyl, the HIARC selected a NOAEL (0.1 mg/kg) from an acute neurotoxicity study based on the following weight of the evidence of the toxicity data:

1) The chronic dog and rat studies yielded a higher NOAEL/LOAEL (dog NOAEL = 0.9 mg/kg, LOAEL = 1.36 mg/kg; rat NOAEL = 1.97 mg/kg, LOAEL = 4.19 mg/kg).

2) The ChEI was not measured at the peak time in chronic studies (dog 2 - 3 hours post feeding ; rat study RBC and plasma at 1, 3, 6, 12, 18 and 24 months and brain ChE levels at 12 and 24 months from 16 hour fasted animals).

3) The NOAEL of 0.1 mg/kg will be protective of chronic (repeat) exposure.

4) The ChEI was reversible as determined in the carbamate reversibility study (i.e., no cumulative toxicity; recovery of clinical signs of ChEI and ChEI occurred within 2 hours post dosing of 1 mg/kg oxamyl); and

5) The NOAEL of 0.1 mg/kg is also protective of any maternal/developmental effects which were seen at 0.8 mg/kg.

Uncertainty Factor (UF): Inspite of use of a study of shorter duration, the HIARC did not recommend any additional factor because the database did not demonstrate cumulative toxicity for the end point of concern. Therefore, use of 100 UF is adequate to account for inter-species extrapolation and for intra-species variability.

Chronic RfD = $\frac{0.1 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.001 mg/kg**

C. Occupational/Residential Exposure

There are no registered residential uses at the present time.

1. Dermal Absorption

A dermal absorption factor is not required since a dermal NOAEL was selected for Short- and Intermediate-Term dermal exposure risk assessment; the use pattern does not indicate long term dermal exposure potential. Therefore, Long-Term dermal risk assessment is not required.

2. Short-Term Dermal - (1-7 days)

Study Selected: 21-Day Dermal Toxicity - Rabbit - **Guideline #:** 82-2

MRID No. 44751201

Executive Summary: In a 21-day dermal toxicity study, groups of 6 male and 6 female HM:(NZW)fBR rabbits were treated with oxamyl technical (96.9%, a.i.) moistened with deionized water by dermal occlusion at doses of 0, 25, 40, 50 or 75 mg/kg/day, for 6 hours a day, 7 days/week. The dosages and the peak time (1 hour post unwrapping) for blood collection was based on pilot studies. No mortality was recorded, and there were no clinical signs indicative of systemic toxicity at any treatment level. No treatment-related dermal irritation was produced. There were no treatment-related effects on body weight, food consumption or food efficiency in either sex of rabbits. Significant inhibition of plasma (29%) and brain (10.7%) cholinesterase was observed in female rabbits at 75 mg/kg/day. In addition, there was inhibition of red blood cell (RBC) cholinesterase in female rabbits treated with 75 mg/kg/day was noticed; although inhibition was statistically not significant, but considered biologically relevant because of magnitude of depression (24%) accompanying statistically significantly plasma and brain cholinesterase depression. In males rabbits, there were no treatment-related changes in the plasma, red blood cell or brain cholinesterase at any dose levels during the study. The female plasma, RBC or brain cholinesterase activity was not statistically significantly changed at 25, 40, or 50 mg/kg/day.

Systemic toxicity was not observed in this study. The **Systemic Toxicity NOAEL = 75 mg/kg/day.**

The **Cholinesterase NOAEL = 50 mg/kg/day, and LOAEL = 75 mg/kg/day,** based on decreased plasma, red blood cell and brain ChE inhibition in females rabbits. In male rabbits, the **NOAEL = 75 mg/kg/day, and LOAEL > 75 mg/kg/day.**

The study is classified as **Acceptable/non-guideline**.

Dose and Endpoint for Risk Assessment: Dermal NOAEL= 50 mg/kg/day based on decrease in plasma, red blood cell and brain ChE levels at 75 mg/kg/day in female rabbits.

Comments about Study and Endpoint: In 1996, the Toxicology Endpoint Selection Committee used 21-Day dermal toxicity study in rabbit (MRID 40827601) for this

exposure duration. In this study the NOAEL was 2.5 mg/kg/day and the LOAEL was 50 mg/kg/day based on decreased plasma, red blood cell and brain ChE levels. In that study the lower NOAEL/LOAEL was observed because of the possible oral ingestion of the test article since animals were not restrained (collared). In the present study (MRID 44751201) oral ingestion was prevented by the use of collars throughout the study duration. Therefore, the NOAEL of 50 mg/kg/day is appropriate for this risk assessment.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 21-Day Dermal Toxicity - Rabbit - §82-2

MRID No. 44751201

Executive Summary: See Short-Term Dermal.

Dose and Endpoint for Risk Assessment: Dermal NOAEL= 50 mg/kg/day based on decrease in plasma, red blood cell and brain ChE levels at 75 mg/kg/day in female rabbits.

Comments about Study and Endpoint: See Short-Term Dermal.

4. Long-Term Dermal (Several Months to Life-Time)

The current use pattern (Oxamyl is registered on terrestrial food and non-food crops, and applied using groundboom, aerial, airblast, chemigation, soil injection, handgun sprayer, and bulb dip equipment at the rate of of 0.25 to 8 lb ai/acre at weekly intervals not to exceed 6 application/year) does not indicate a potential for long-term exposure. Therefore, a dose and endpoint was not selected for this exposure scenario.

5. Inhalation Exposure (Any Time Period)

Study Selected: Acute Inhalation Toxicity **Guideline #:** Non-Guideline
MRID No.: 45155801

Executive Summary: In an acute nose only inhalation study, 10 Crl:(SD) IGS BR rats per sex per group were exposed to 0.0049 mg/L or 0.024 mg/L of aerosolized oxamyl dust for 4 -hours (MRID# 45155801). Test atmospheres were measured gravimetrically. Particle sizes generated had a MMAD ranging from 0.85 to 1.2 µm. Immediately following exposure, all rats were sacrifice and blood and brain samples were collected for cholinesterase analyses.

No deaths in either sex or at either dose level were seen during or immediately after exposure prior to sacrifice. Tremors and lethargy was seen in most rats following exposure. Other clinical signs immediately following exposure were wet/stained fur, ocular/nasal discharge, and diarrhea. At the 0.0049 mg/L, these latter clinical signs were stated to be similar to control incidences, however, clinical signs by group or individual signs were not reported.

Only initial body weights were determined, since animals were sacrifice immediately after exposure.

Biologically and statistically significant plasma (PCHEI), erythrocyte (ECHEI) and brain cholinesterase inhibition (BCHEI) occurred in males and ECHEI and BCHEI occurred in females at both dose levels. PCHEI was not significant in females at the LDT. In males at 0.0049 and 0.024 mg/L, PCHEI was 12% and 72%, ECHEI was 28% and 72%, and BCHEI was 15% and 68%, respectively. In females at 0.0049 and 0.024 mg/L, PCHEI was 6.5% and 76%, ECHEI was 29% and 73%, and BCHEI was 9% and 67%, respectively.

The LOAEL was the LDT of 0.0049 mg/L base on biologically and statistically significant decreases in PCHEI, ECHEI, and BCHEI in males and females. PCHEI was not significant for females at the LDT. Thus there was a NOAEL for females, but not for males.

The study is acceptable as a non-guideline (NG) study of oxamyl induced cholinesterase inhibition through 4-hour acute inhalation exposure.

Dose and Endpoint for Risk Assessment: 0.000016 mg/L based on decreased plasma, red blood cell and brain ChE levels in male and female rats at the lowest concentration tested.

Comments about Study and Endpoint: Since a LOAEL was used, a margin of exposure (MOE) of 300 is required, i.e., a conventional MOE of 100 and an additional 3X for use of a LOAEL. The MOE of 300 is required for short-term and intermediate-term exposure risk assessment. The use pattern does not indicate a potential for long-term exposure.

D. Margins of Exposure for Occupational Exposures

A MOE of 100 is adequate for occupational dermal and a MOE of 300 is required for inhalation exposure risk assessments. There are no registered residential uses at this time.

E. Recommendation for Aggregate (Food + Water + Residential) Risk Assessments

There are no registered residential uses. Therefore aggregate exposure risk assessment will be

limited to food plus water only.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study-Rats §83-5

MRID No. 41963101

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 41963201) oxamyl (97.1%, a.i.) was administered in diet to 62 Crl:CD®BR rats/sex at dose levels of 0, 25, 50, 100 or 150 ppm (0, 0.992, 1.97, 4.19, or 6.99 mg/kg/day for males and 0, 1.32, 2.69, 6.73 or 11.1 mg/kg/day for females, respectively) for 2 years. An interim sacrifice of 10 rats/sex/dose was conducted at 12 months. Body weight, food consumption, food efficiency, hematology, clinical chemistry, uranalysis, and organ weights were done.

Treatment with oxamyl did not effect mortality, food consumption, food efficiency, hematology clinical chemistry, and urinalysis. At 100 and 150 ppm the incidence of hyperactivity and swollen paws/legs in males and hyperactivity and skin sores in females increased significantly ($P < 0.05$). The incidence of hyperactivity at 0, 25, 50, 100 and 150 ppm in males/females was 27%/17%, 37%/23%, 32%/20%, 52%/50% and 63%/73%, respectively. The incidence of swollen legs/paws in mid and high-dose males was 29% and 34%, respectively, compared to 11% in controls. In high-dose females the incidence of swollen paws was 23% compared to 5% in controls. High dose females exhibited a high incidence of alopecia (56%; $P < 0.05$). Females also exhibited an increased incidence of skin sores or scabs; the incidence at 100 and 150 ppm, was 61% and 82% , respectively, compared to 39% in controls. Mean body weights and body weight gains were significantly lower in males and females at two higher doses during the first year of study. In males at 100 and 150 ppm the mean body weight gains decreased 10% and 25% ($P < 0.05$), respectively, compared to controls. At these dose levels the female body weight gains were depressed by 27% and 37%, respectively, compared to the controls. The decreased body weights and body weight gains in males and females were considered secondary to hyperactivity since neither the food consumption nor the food efficiency was affected in these test groups. Ophthalmologic evaluations of male rats revealed that 3 of 27 in the 100 ppm group and 4 of 31 in the 150 ppm group with pale ocular fundi. In female at 150 ppm 4 of 34 rats were observed with bilateral iris atrophy. Histopathologically, by study termination the high-dose females exhibited ($P < 0.05$) a higher incidence of bilateral retinal photo cellular atrophy. This finding was not observed at one year sacrifice in females. At 100 and 150 ppm, in males plasma ChE levels significantly decreased during the study which ranged from 15 - 48%, compared to the controls. In females, at these dose levels, plasma ChE was inhibited 38% and 69% ($P < 0.05$), respectively, during the first month of treatment. The red blood cell and brain ChE levels in males and females were not affected at any dose level. The results did not show any treatment-related increase in tumor incidence.

Based on the effects of oxamyl on body weights, eyes lesions, hyperactivity, plasma cholinesterase inhibition, and retinal photo receptor cell atrophy, the highest dose tested (150 ppm) appeared to be sufficiently high enough for testing the chronic toxicity and carcinogenicity of Oxamyl.

The **systemic toxicity NOAEL = 50 ppm** (1.97 mg/kg/day for males and 2.69 mg/kg/day for females) and the **LOAEL = 100 ppm** (4.19 mg/kg/day for males and 6.73 mg/kg/day for females) based on hyperactivity, swollen legs/paws, and skin sores, decreased body weights and body weight gains, increased incidence of ocular fundi in males and females and inhibition of plasma cholinesterase in males.

CLASSIFICATION: The study is classified as **Acceptable/Guideline** and meets the requirements for a combined chronic toxicity/carcinogenicity study in rodent (83-5).

Discussion of Tumor Data: **There was no evidence of carcinogenicity**.

Adequacy of the Dose Levels Tested: Based on the effects of oxamyl on body weights, eyes lesions, hyperactivity, plasma cholinesterase inhibition, and retinal photo receptor cell atrophy, the highest dose tested (150 ppm) appeared to be sufficiently high enough for testing the chronic toxicity and carcinogenicity of Oxamyl.

2. Carcinogenicity Study-Mice §83-2b

MRID No. 00076813

Executive Summary: In a carcinogenicity study (MRID 00076813) oxamyl (97.1%, a.i.) was administered in diet to 80 - 88 CD-1 mice/sex at dose levels of 0, 25, 50, or75/100 ppm (conversion: 0, 3.75, 7.5 or 15/11.25 mg/kg/day for males and females, respectively) for 18 months. The 100 ppm dose was reduced to 75 ppm due to mortality in the mid- and high-dose groups during the initial phase of the study; however, timing was not available. Body weight, food consumption, hematology, and organ weights were done.

Treatment with oxamyl did not effect mortality, food consumption, and hematology. Body weight decrements in males persisted throughout the study period. During week 11, the body weights of 50 and 75 ppm males decreased 5.5% ($P < 0.05$) each, respectively, compared to controls. In female mice body weights decreased early in the study, however, were sporadic and were not statistically significant. Organ weights or histopathology was remarkable. Exposure to oxamyl at 75 ppm did not increase in tumor incidence.

Based on the effects of body weights in males and mortality in both sexes during the initial phase of the study, the highest dose tested (75 ppm) appeared to be sufficiently high enough for testing the carcinogenic potential of oxamyl.

The **systemic toxicity NOAEL = 25 ppm** (3.75 mg/kg/day) and the **LOAEL = 50 ppm** (7.5 mg/kg/day) based on decreased body weights in males and mortality in males and females during the initial phase of the study.

CLASSIFICATION: The study is classified as **Acceptable/Guideline** and meets the requirements for a Carcinogenicity study in rodent (83-2).

Discussion of Tumor Data: **There was no evidence of carcinogenicity**.

Adequacy of the Dose Levels Tested:. Based on the effects of body weights in males and mortality in both sexes during the initial phase of the study, the highest dose tested (75 ppm) appeared to be sufficiently high enough for testing the carcinogenic potential of oxamyl.

3. Classification of Carcinogenic Potential:

At the August 15, 1996 meeting the HED RfD Peer Review Committee classified oxamyl as a **"Group E"** chemical based on the lack of evidence of carcinogenicity in male and female mice as well as in male and female rats.. The HIARC concurred with the previous classification.

IV. MUTAGENICITY

GENE MUTATION

1) *Salmonella typhimurium* reverse gene mutation assay (MRID 40606509; HED Doc. # 006891& 007077): The test is in *S. typhimurium* strains TA1535, TA1537, TA98 and TA100 at doses ranging from 50 to 10,000 µg/plate with or without S9 activation. The test is negative in all strains and concentrations. This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

2) Chinese hamster ovary (CHO) HGPRT forward gene mutation assay (MRID 40606510; HED Doc. # 006891& 007077): The test is negative in independently performed trials up to concentrations causing < 80% decrease in cell viability (1200 µM -S9; 700 µM +S9). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

CHROMOSOMAL ABERRATIONS

3) In vitro CHO cell chromosome aberration Assay (MRID 40606507; HED Doc. # 006891& 007077): The test was negative up to cytotoxic concentrations (# 70 µg/mL -S9; 700 µg/mL +S9). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

OTHER MUTAGENIC MECHANISMS

4) DNA damage/repair in *Bacillus subtilis* rec assay (MRID 00049594; HED Doc. # 005858): The test was negative up to the highest dose tested (2000 µg/disc -S9). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

5) In vitro unscheduled DNA sysnthesis in primary rat hepatocytes (MRID 40606508 & 41096001; HED Doc. # 006891& 007595): The test is negative up to cytotoxic concentrations (# 5 nM). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

V. FQPA CONSIDERATIONS

1. Neurotoxicity:

(1) Acute Neurotoxicity - Rat

In an acute oral neurotoxicity study (MRID Nos: 44254401, 44420301 & 44740701), single gavage doses of oxamyl (98.3% a.i.; Sample No.: 16995-02) in deionized water were administered to groups of Crl:CD rats (42/sex/dose). Males received 0, 0.1, 1.0, or 2.0 mg/kg and females received 0, 0.1, 0.75, or 1.5 mg/kg. Twelve rats/group were designated as neurotoxicity subgroup animals. All twelve of these rats/group were used for Functional Observational Battery (FOB) and Motor Activity (MA) assessments on days 1, 8, and 15. Body weight and clinical signs were also recorded for these animals. Six of the rats/group were euthanized for *in situ* perfusion. Thirty rats/group were designated as the clinical pathology group and were utilized for blood and brain collection for evaluation of cholinesterase levels.

One high-dose male died on day 1. High-dose males had significantly ($p<0.05$) decreased mean body weight gain for days 1-2. Similarly, mid-dose males and high-dose females also exhibited lower (n.s.) body weight gains. Decreased food consumption (n.s.) was also observed in mid- and high-dose males.

Statistically ($p<0.05$) and biologically significant dose related decreases in blood and brain cholinesterase activity were observed in mid- and high-dose males and females on day 1. Mean decreases were generally $40%. By day 2, decreases in cholinesterase activity were no longer biologically significant. No toxicologically significant decreases in cholinesterase activity were observed in any animals after day 1 or in low-dose males and females at any time point.

Clinical signs and FOB effects, consistent with decreased cholinesterase activity, were observed 30-60 minutes post-exposure in the mid- and high-dose males and females. Observations included soiled fur, lacrimation, salivation, slow righting reflex, abnormal gait, tremors, impaired locomotion, no response to tail pinch, limb splay, incoordination, labored breathing, and decreased forelimb and hindlimb grip strength. Other effects, including posture, palpebral closure, docile behavior, and decreased motor activity, were likely due to lethargy and malaise secondary to decreased

cholinesterase activity. No treatment-related clinical signs or FOB effects were observed in low-dose animals or after day 1. **Therefore, the RBC, plasma and brain ChE inhibition NOAEL = 0.1 mg/kg/day for males and females and LOAEL = 1.0 mg/kg/day in males and 0.75 mg/kg/day in females.**

No treatment-related gross effects or histopathology were observed.

Under the conditions of this study, the systemic/neurotoxicity LOAEL is 1.0 mg/kg for male rats and 0.75 mg/kg for female rats based on clinical signs, FOB effects, and decreased blood and brain cholinesterase activity. The NOAEL is 0.1 mg/kg.

This acute oral neurotoxicity study is classified **acceptable (guideline)**. This study does satisfy the guideline requirement for an acute oral neurotoxicity study (81-8) in rats.

(2) Subchronic Neurotoxicity - Rat

In a subchronic oral neurotoxicity study (MRID 44504901), 42 Crl:CD^{R}(SD)BR rats/sex/exposure group were administered Oxamyl Technical (purity, 98.3%; Haskell sample number 16995-02) at concentrations of 0, 10, 30, or 250 ppm (equivalent to 0, 0.564, 2.10, or 14.9 mg/kg/day for male rats and 0, 0.679, 2.40, or 19.9 mg/kg/day for female rats, respectively) in the diet. The 30 and 250 ppm concentrations were reduced from 100 and 300 ppm, respectively, on day 7 of administration due to toxic effects including tremors and weight loss. Twelve rats/sex/exposure group were assigned to the neurotoxicity group and underwent functional observational battery (FOB) and motor activity (MA) testing prior to dietary administration and during weeks 4, 8, and 13. Ten rats/sex/exposure group were sacrificed on days 27 and 55 and at termination of the study for cholinesterase activity determinations. Six rats/sex/exposure group (from the neurotoxicity group) were perfused for neuropathology at study termination.

All animals survived to scheduled termination. At the end of 90 days, body weights of male and female rats receiving 250 ppm in the diet were significantly depressed by 24% and 10%, respectively ($p<0.05$). Decreases in body weights correlated with decreased food consumption in males and decreased food efficiency in both sexes. Exposure-related clinical signs (tremors, abnormal gait or mobility, hunched-over posture, exophthalmos, ptosis, hyperactivity, piloerection, colored discharge from the eyes, hyperactivity and lacrimation) were present in one or both sexes administered 250 ppm in the diet but not in animals administered 30 or 10 ppm. During the FOB, significant changes in incidences of ptosis, piloerection, abnormal gait, pupillary response to light, and hindlimb grip strength were observed in either male and/or female rats administered 250 ppm. At the end of the study, the mean plasma, red blood cell and cortical (brain) ChE levels were decreased by 24, 48 and 40%, respectively in males and 60, 55, and 51%, respectively in females, compared to controls. Decreases in brain and blood cholinesterase activity correlated with the presence of clinical signs and changes in FOB parameters in the 250 ppm group. Generally, the

magnitude of ChE inhibition was greater in females than males; and there was no cumulative effect with time. Motor activity - duration and number of movements - was not significantly affected at any concentration. No Oxamyl-related neuropathological changes were observed in any exposure group.

Under the conditions of this study, the **Systemic Toxicity LOAEL is 250 ppm (14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively), based on decreases in body weights and food efficiency of both sexes. The NOAEL is 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively).**

The LOAEL for neurobehavioral effects is 250 ppm (14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively) based on decreases in plasma, RBC and brain ChE activity, clinical signs consistent with cholinesterase inhibition, and changes in incidences of FOB parameters such as increases in ptosis, piloerection, and abnormal gait and decreases in pupillary response to light and hindlimb grip strength. The NOAEL is 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively.

This study is classified **acceptable** and satisfies the guideline requirement for a subchronic oral neurotoxicity study (82-7) in rats.

2. Developmental Toxicity

(i) Rat

In a developmental toxicity study (MRIDs 40859201 & 44737501) oxamyl (97.2%) was administered by gavage to groups of pregnant Charles River (CD) BR rats (25/group) at dose levels of 0, 0.2, 0.5, 0.8, and 1.5 mg/kg from gestation days 7 to 16. On day 22, the fetuses were removed, and the dams were sacrificed.

There were no mortalities or treatment-related gross abnormalities were reported. Maternal toxicity was observed at the 0.8 mg/kg/day, as decreased body weight gain (21%; $P < 0.05$), decreased food consumption (10%; $P < 0.05$) and increased incidence of tremors (4/25) associated with cholinesterase inhibition. The decreased body weight gain and food consumption and increased incidence of tremors were dose-related. At 1.5 mg/kg/day dose the body weight gains and food consumption decreased 30% and 16% ($P < 0.05$), respectively, compared to controls. At this dose increased number of dams showed statistically significant ($P < 0.05$) increase in signs of diarrhea, eye discharge, salivation, tremors, and wet legs, perineal and underbody. Treatment had no effect on the reproductive parameters and/or fetal malformations or variations. A dose-related decrease in fetal body weights was seen and decrease was statistically significant ($P < 0.05$) at doses 0.5 mg/kg and above. The fetal weights at 0.2, 0.5, 0.8, and 1.5 mg/kg, decreased 1.6%, 3.9%, 6.75% and 6.9%, respectively, compared to the controls.

Under the conditions of this study, **Maternal Toxicity NOAEL = 0.5 mg/kg/day and the LOAEL = 0.8 mg/kg/day**, based on decreased body weight gains, decreased food consumption and increased incidence of tremors.

The **Developmental Toxicity NOAEL = 0.2 mg/kg/day and the LOAEL = 0.5 mg/kg/day**, based on dose-related decreased in the fetal body weight.

CLASSIFICATION: The study is classified as Acceptable/Guideline and satisfies the data requirements for developmental toxicity study (83-3) in rat.

(ii) Rabbit

In a developmental toxicity study (MRID 00063009) oxamyl (97.1%) was administered by gavage to groups of pregnant (artificial insemination) New Zealand White Rabbits (17/group) at dose levels of 0, 1, 2, and 4 mg/kg from gestation days 6 through 19. On day 29, the fetuses were removed, and the dams were sacrificed. Fetal weight and length were measured and soft tissues and skeletal abnormalities recorded. Also recorded were number of corpora lutea, number of implantation, resorptions, dead and live fetuses.

There were no mortalities or gross abnormalities were reported. During the treatment period days 6 - 19, maternal toxicity was observed at 2 and 4 mg/kg/day, as decreased body weight gains of 61.5% and 67.2% ($P < 0.05$), respectively, compared to controls. At 1 mg/kg/day body weight gains decreased 28.8%, compared to the controls, but the decreases were statistically not significant. A slightly higher incidence of resorption in the mid- and high-dose groups were observed. The mean number of resorptions at 2 and 4 mg/kg/day were 1 and 1.2, respectively, compared to 0.8 in the controls.

Under the conditions of this study, **Maternal Toxicity NOAEL = 1 mg/kg/day and the LOAEL = 2 mg/kg/day**, based on decreased body weight gains.

The **Developmental Toxicity was not observed up to the highest dose tested. The developmental NOAEL = 4 mg/kg/day.**

CLASSIFICATION: The study is classified as Acceptable/Guideline and satisfies the data requirements for developmental toxicity study (83-3b) in rabbit.

3. Reproductive Toxicity:

In a two-generation reproduction study (41660801), Crl:CD^{R}BR rats were fed oxamyl (97.1%, a.i.) in the diet at dosage levels of 0, 25, 75, or 150 ppm (approximately 0, 1.7, 5.2 or 11.6

mg/kg/day for males and 0, 2.0, 6.6 or 15.8 mg/kg/day for females, respectively). Systemic/Developmental toxicity was observed in both sexes and generations at 75 ppm and above as significantly decreased food consumption (F_0 males and females 14.6 - 15.7%, F_1 males and females 9.9%- 16.8%), body weight (F_0 males and females 5 - 9%, F_1 males and females 7 - 20%) and body weight gain (F_0 males and females 14.6 - 20.7%, F_1 males and females 13 - 13.7%). In addition, at 150 ppm, a significantly increased incidence of clinical signs (hyperactivity, skin sores and alopecia) was observed.

Based on these results, the **NAOEL for systemic/developmental toxicity was 25 ppm** (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); **the LOAEL was 75 ppm** (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

Offspring toxicity was observed at 75 and above in both generations as significantly decreased body weight during lactation in both generations (2 - 7.6%). In addition, at 150 ppm, the number of live pups per litter and the viability index decreased 15.7 - 16.4% and 21 - 43%, respectively. Based on these results, **the NOAEL for offspring toxicity was 75 ppm** (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively); **the LOAEL was 150 ppm** (approximately 11.6 and 15.8 mg/kg/day for males and females, respectively).

CLASSIFICATION: The study is **Acceptable** and satisfies the guideline requirements (83-4) for a Reproduction Toxicity Study in Rats.

4. Additional information from the literature

There are no additional neurotoxicity studies or developmental neurotoxicity studies via inhalation or any other routes from the published literature.

5. Determination of Susceptibility

In the prenatal developmental toxicity study in rats, the developmental NOAEL (0.2 mg/kg) was lower than the maternal NOAEL (0.5 mg/kg/day) indicating a quantitative evidence of susceptibility. The HIARC, however, concluded that this was not a true indication of increased susceptibility since the decrease in fetal weights (3.9%) was seen in the fetuses of dams at 0.5 mg/kg/day that also exhibited decreases (9%) in body weight gain and food consumption as well as clinical signs (tremors) of toxicity. The dose of 0.5 mg/kg/day was selected as the maternal NOAEL since the observed decreases in body weight (9%) were not determined to be statistically significant. In addition, at higher doses the decreases in fetal body weights corroborated with statistically significant decreases in maternal body weights and food consumption and clinical signs with increasing doses. Thus the data indicated that the decreases in fetal weights are not an indication of increased susceptibility, but occurred due to maternal toxicity (characterized as decreases in body

weight gain).

In the developmental toxicity study in rabbits, no developmental toxicity was seen at the highest dose tested. In the two-generation reproduction study in rats, decrease in pup viability and decreased pup body weights observed at the highest dose tested is of no concern due to significantly decreased in maternal body weights during the lactation.

6. Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-evidence considerations, the HIARC **did not recommend** a developmental neurotoxicity study in rats for oxamyl.

- Clinical signs and FOB observations in acute and subchronic neurotoxicity studies were not associated with any neuropathology.
- Tremors seen in 1-year dog studies were not associated with any neuropathology. These signs may be due to cholinergic effects of oxamyl.
- Even though tremors were observed in the maternal animals in developmental rat study, there was no evidence of CNS malformations observed either in the rat or rabbit developmental toxicity studies.
- Eventhough hyperactivity was seen in 2-generation reproduction study, there was no apparent evidence of behavioral clinical observations in pups.
- The HIARC concluded that bilateral iris and retinal photoreceptor cell atrophy observed in female SD rats in a 2-year chronic study may be due to aging of animals.

VI. HAZARD CHARACTERIZATION

Oxamyl, ethanimidothioic acid, 2-(dimethylamino)-N-{[(methylamino)carbonyl]oxy}-2-oxo-, methyl ester; DPX-D1410-196; DPX-D1410-196 Technical; methyl2-(dimethylamino)-N-{[(methylamino)carbonyl]oxy}-2-oxo-ethanimidothioate; methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate, is a water soluble carbamate insecticide (nematicide/acaricide) currently registered under terrestrial food and non-food category for use on field crops, vegetables, fruits and ornamentals. The Caswell number of oxamyl is 561A. The CAS Number of oxamyl is 23135-22-0.

With the exception of the oral and inhalation LD_{50} studies (Category I & II, respectively), other acute studies have demonstrated oxamyl has low acute toxicity by other routes of administration (Category III & IV). Oxamyl is a mild eye irritant. It is not a skin sensitizer or a skin irritant in animal studies. In an acute neurotoxicity study in rats, neurobehavioral effects (FOB findings and numerous clinical signs) were observed at a dose level of 0.75 mg/kg/day (females) and 1 mg/kg/day (males). In the dietary subchronic neurotoxicity study the same types of findings were observed at higher doses males (14.9 mg/kg) and females (19.9 mg/kg) with a NOAEL of 2.1 mg/kg (males). Neurotoxic effects were also seen in maternal animals in the rat developmental toxicity study and also seen in chronic dog studies. No neuropathological

findings were associated with neurotoxicity effects in the above mentioned studies, except retinal photoreceptor cell atrophy seen in females in 2-year chronic rat study, which was considered within historical background and due to aging of the rats.

No dermal toxicity was observed in 21-day rabbit dermal toxicity (MRID 44751201); however, systemic toxicity related to blood and brain ChEI was observed in females at 75 mg/kg dose level. No developmental toxicity was seen at the highest dose tested (4 mg/kg) following in utero exposure to rabbits. Following in utero exposure to rats, decreased in fetal body weights were seen in the presence of maternal toxicity. In the two-generation reproduction study off-spring toxicity was seen only in the presence of parental/systemic toxicity at the highest dose tested (5.2 mg/kg). Therefore, there was no indication of increased susceptibility following exposure to oxamyl.

Acute RfD of 0.001 mg/kg/day was derived from the Acute Neurotoxicity Study in rats. This study was considered appropriate by the committee because neurobehavioral effects are presumed to occur after a single exposure (dose).

Generally, a NOAEL/LOAEL from the chronic study is selected for establishing the chronic RfD. However, for Oxamyl, the HIARC selected a NOAEL from an acute neurotoxicity study based on weight of the evidence of the toxicity data such as the chronic dog and rat studies which yielded a higher NOAEL/LOAEL compared to the acute neurotoxicity study, the measurement of ChEI was not conducted at the peak time in chronic studies, the acute NOAEL (0.1 mg/kg) is also protective of any maternal/developmental effects and chronic exposure (repeated), and ChEI was reversible (not cumulative) as determined in the carbamate reversibility study. Therefore, there is high confidence in the chronic RfD derived from the acute neurotoxicity study in rat.

At the August 15, 1996 meeting the HED RfD Peer Review Committee classified oxamyl as a "**Group E**" chemical based on the lack of evidence of carcinogenicity in male and female mice as well as in male and female rats. The HIARC concurred with the previous classification.

In *in vitro* studies, oxamyl is not mutagenic in the Ames test (bacteria), not mutagenic in mammalian cell culture (CHO), did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, negative for inducing DNA damage/repair, and does not cause unscheduled DNA damage in primary rat hepatocytes. These acceptable studies satisfy the pre-1991 mutagenicity guideline requirements.

VII. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158.

VIII. RECOMMENDATION FOR ADDITIONAL STUDIES

None.

IX. ACUTE TOXICITY

Acute Toxicity Profile of Oxamyl

GDLN	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	00063011	LD_{50} = 3.1 mg/kg (M); 2.5 mg/kg (F)	I
81-2	Acute Dermal (Rabbit)	40606501	LD_{50} > 5000 mg/kg (M) >2000 mg/kg (F) For abraded skin 90 mg/kg produced death with 50% a.i. in water	IV
81-3	Acute Inhalation	00066902	LC50 = 0.064 mg/L (4 hr) 0.17 mg/L (M) 0.12 mg/L (F) (I hr)	II
81-4	Primary Eye Irritation	00066894	Marked pupillary constriction, conjunctival irritation, reversible by 7 days	III
81-5	Primary Skin Irritation	40606501	Mild erythema and edema. Clear by day 5, except in one rabbit that clear by day 12	IV
81-6	Dermal Sensitization	00066900	4/7 animals died (25% test material) 1/5 animals died (intradermal injection) Effects seen on the test site were slight. Extreme toxicity makes dermal sensitization study relatively unimportant	Not a skin sensitizer (25% test material)

81-8	Acute neurotoxicity-hens 20 and 40 mg/kg as 1% suspension; the hens were protected with 0.5 mg/kg atropine. **Invalid study**	00066893	Clinical signs included: depression, lethargy, ruffled feathers, ataxia, incoordination, and slight respiratory difficulty. 12 hr. Later all symptoms disappeared. No compound-related histological changes were found. No deaths occurred.	NA

X SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	Acute Neurotoxicity NOAEL=0.1 UF=100	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat (MRID# 44254401, 44420301 & 44740701
	Acute RfD = 0.001 mg/kg		
Chronic Dietary	NOAEL=0.1 UF=100	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat (MRID# 44254401, 44420301 & 44740701
	Chronic RfD = 0.001 mg/kg/day		
Short- Term (Dermal)	Dermal NOAEL=50 UF=100	LOAEL = 75 mg/kg/day is based on plasma, red blood cell and brain ChEI in females	21-Day Dermal Toxicity - Rabbit (MRID# 44751201)
Intermediate- Term (Dermal)	Dermal NOAEL=50 UF=100	LOAEL = 75 mg/kg/day is based on plasma, red blood cell and brain ChEI in females	21-Day Dermal Toxicity - Rabbit (MRID# 44751201)
Long-Term (Dermal)	Based on the use pattern (applied using groundboom, aerial, airblast, chemigation, soil injection, handgun sprayer, and bulb dip equipment at the rate of 0.25 to 8 lb ai/acre, may be applied at weekly intervals up to a maximum of 6 applications/crop cycle), this risk assessment is not required.		
Inhalation (Short & Intermediate)	Acute Inhalation LOAEL=0.0049 mg/L UF=300	LOAEL = 0.0049 mg/L is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in rats	Acute inhalation - Rat (MRID# 4515801)
Inhalation (Long-Term)	Based on the use pattern (applied using groundboom, aerial, airblast, chemigation, soil injection, handgun sprayer, and bulb dip equipment at the rate of 0.25 to 8 lb ai/acre, may be applied at weekly intervals up to a maximum of 6 applications/crop cycle), this risk assessment is not required.		